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REVISIÓN

Role of altered immune cells in liver diseases: a review

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KEYWORDS
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Abstract Immune cells play an important role in controlling liver tumorigenesis, viral hepatitis, liver fibrosis and contribute to pathogenesis of liver inflammation and injury. Accumulating evidence suggests the effectiveness of natural killer (NK) cells and Kupffer cells (KCs) against viral hepatitis, hepatocellular damage, liver fibrosis, and carcinogenesis. Activation of natural killer cells provides a novel therapeutic strategy to cure liver related diseases. This review discusses the emerging roles of immune cells in liver disorders and it will provide baseline data to scientists to design better therapies for treatment.

PALABRAS CLAVE
Hígado;
Cirrosis;
Células NK;
Células dendríticas;
Células de Kupffer

Revisión sobre el papel de los inmunocitos alterados en las enfermedades hepáticas

Resumen Los inmunocitos o células inmunitarias desempeñan un papel importante en el control de la carcinogénesis hepática, la hepatitis vírica, la fibrosis hepática y contribuyen a la patogénesis de la inflamación y la lesión hepáticas. La creciente evidencia sugiere la efectividad de los linfocitos citolíticos naturales (NK, *natural killer*) y las células de Kupffer (KC, Kupffer cells) frente a la hepatitis vírica, la lesión hepatocelular, la fibrosis hepática y la carcinogénesis.

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La activación de linfocitos citolíticos naturales ofrece una nueva estrategia terapéutica para curar enfermedades relacionadas con el hígado. Esta revisión trata de las nuevas funciones de los inmunocitos en los trastornos hepáticos y ofrecerá datos básicos a los científicos para diseñar mejores terapias para el tratamiento.

Introduction

Liver is the metabolic centre of organism controlled by central nervous system. Its anatomic localization and specific tissue structure indicates its defensive role in organism. Approximately 80% of liver cells are hepatocytes. Non-hepatocytes include 40% endothelial cells 20% Kupffer cells, 20% lymphocytes, 20% stellate cells, and biliary cells. Natural killer cells make up 50% of liver population that reside in liver sinusoids. The multitude of cells makes this organ play active role in peripheral immune tolerance of the organism using transforming growth factor-β and haemopoetic cells. The fifth most common cancer in the world is liver cancer, 90% of which is hepatocellular carcinoma (HCC) [1] and the better understanding of liver's immunological processes will provide insight into the role of immune tolerance mechanisms and its contribution in the development of autoimmune diseases and chronic viral infections of liver.

Natural killer cells inhibit liver fibrosis, viral infection and tumor cells growth. The liver immune system is properly equipped with liver immune cells that achieve the critical task of protection against metastatic cells, pathogens, and foreign antigens by coordinating with anti-microbial components (inflammatory cytokines, chemokines, acute phase proteins, complement). Liver plays its role as a buffer between systematic circulation and the contents of gut and about 80% of blood is supplied from gut into liver through portal vein. This blood is rich in harmless environmental antigens, microflora of gut, and dietary elements. Liver must endure immunogenic load by providing immunosurveillance for malignant cells and pathogenic infections.[2,3] Innate immune cells of liver such as KCs, monocytes, dendritic cells (DCs), NK cells, natural killer T cells (NKT) cells, and neutrophils produce cytokine and initiate inflammation.[4] We will briefly discuss the potential roles of immune cells in the pathogenesis of liver related disorders.

Natural killer (NK) and natural killer T (NKT) cells

The lymphocytes present in liver are enriched in NK and NKT cells that are key regulators of antitumor defenses, antiviral defenses, and pathogenesis of chronic liver disease. These cells account for 25-40% of total intrahepatic lymphocytes. NK cells have some peculiar functional and phenotypic properties such as specific cytokine profiles, and TRAIL-dependent cytotoxicity.

Decline in NK/NKT cells greatly increases tumor metastatsis of liver and enhancement of NK/NKT cells weakens it,[5,6] both type of cells produce significant quantity of cytokines that stimulate adaptive immune response and help in removal of food antigens, toxins, and pathogens. The role of NKT cells play dominant role as anti-tumor agent by inhibiting liver fibrosis through suppression of hepatic stellate cells activation.[7,8] NK and NKT cells play an important role in pathogenesis of liver inflammation and injury, liver fibrosis and tumorigenesis. Several studies demonstrate that NK and NKT cells control viral hepatitis.[9–12] The mechanisms behind this enrichment and peculiar characteristics of liver NK cells are still not completely elucidated however, effects may be attributed to both cross talk between NK cells and other liver cell types as well as high hepatic expression levels of diverse NK cell-recruiting chemokines.[13,14] NK cells produce diverse cytokines e.g, interferon-gamma (IFN-γ) and kill target cells (Fig. 1).

The opposing signals of stimulatory and inhibitory receptors on NK cells and their association with analogous ligands bound to target cells determines the potential of NK cells to kill target cells.[15] Alterations that occur as a result of signal expression of receptors of NK cells and their interaction with ligands present on liver cells contribute to pathogenesis of liver diseases.[16] NK cells are activated by cytokines e.g, IFN and interleukins (ILs), IFN-α, IFN- β, IL-12, IL-15, IL-18 and several other related cytokines during acute HCV infection.[17] These activated NK cells act as key contributors in prevention of hepatitis C virus (HCV) either by stimulating adaptive immunity or by killing HCV infected liver cells.[18,19] IFN-α acts as powerful NK cell activator and cures viral hepatitis by suppressing tumor formation and liver fibrosis. The anti-tumor, anti-fibrotic, and anti-viral effects of IFN-α therapy are stimulated by activation of NK cells. In addition to IFN-α, there are other NK cell activators like IL-12 and IL-18 that have been proved effective against liver carcinogenesis in animal models.[20,21]

NK cells provide protection against HCV infection because lot of evidences have suggested that selective impairment of NK cell is cause of chronic HCV infection.[22] NK cells also increase NK cell ADCC (antibody-dependent cell-mediated cytotoxicity) and target cancers and tumor cells.[23] Another study demonstrated that NK cell cytotoxicity against tumor cells is increased by blockade of NK cell inhibitory receptors and monoclonal antibodies such as rituximab, IPH-2101 that block killer-cell immunoglobulin-like receptor to treat hematological cancers, this strategy is currently in phase II clinical trials.[24,25] Therefore, blockage of NK cell inhibitory receptors, targeting of NK cells to increase ADCC, and activation of NK cells by cytokines all form the basis of therapeutic strategies against hepatocellular carcinoma (HCC). Adoptive transfer of activated NK cells isolated from donor

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